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DATE: Tuesday, December 28, 2004

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☐	L4	L1 with L2	33
☐	L3	L1 and L2	101
☐	L2	plasma concentration	12051
☐	L1	oxybutynin	695

END OF SEARCH HISTORY

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(FILE 'HOME' ENTERED AT 15:12:26 ON 28 DEC 2004)

FILE 'MEDLINE, HCAPLUS' ENTERED AT 15:12:49 ON 28 DEC 2004

L1	1205	S	OXYBUTYNIN
L2	11	S	L1 AND PHARMACEUTICALLY ACCEPTABLE SALT
L3	20663	S	PLASMA CONCENTRATION
L4	10	S	L1 AND L3
L5	0	S	L2 AND L3

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 NEWS  7  DEC 09   12 databases to be removed from STN on December 31, 2004
 NEWS  8  DEC 15   MEDLINE update schedule for December 2004
 NEWS  9  DEC 17   ELCOM reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  10 DEC 17   COMPUAB reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  11 DEC 17   SOLIDSTATE reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  12 DEC 17   CERAB reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  13 DEC 17   THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB

 NEWS EXPRESS  OCTOBER 29 CURRENT WINDOWS VERSION IS V7.01A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
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=> s oxybutynin
L1         1205 OXYBUTYNIN

=> s l1 and pharmaceutically acceptable salt
L2           11 L1 AND PHARMACEUTICALLY ACCEPTABLE SALT

=> s plasma concentration
L3        20663 PLASMA CONCENTRATION
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=> s L1 and L3
L4 10 L1 AND L3

=> d l4 1-10 ibib abs

L4 ANSWER 1 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2004558555 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15530134
TITLE: Effect of antacid on the pharmacokinetics of extended-release formulations of tolterodine and **oxybutynin**.
AUTHOR: Sathyan Gayatri; Dmochowski Roger R; Appell Rodney A; Guo Cindy; Gupta Suneel K
CORPORATE SOURCE: Department of Clinical Pharmacology, ALZA Corporation, Mountain View, California, USA.
SOURCE: Clinical pharmacokinetics, (2004) 43 (14) 1059-68. Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20041109
Last Updated on STN: 20041220
AB BACKGROUND: In general, extended-release (ER) formulations are designed to prolong the duration of efficacy and reduce the adverse effects of a drug. These formulations often contain the entire daily dose in a single tablet. Therefore, failure of the ER mechanism not only diminishes the desired benefits, but may temporarily expose the patient to drug concentrations higher than those released from a conventional tablet. In this study we determined whether pH has an effect on drug release from the ER formulations of **oxybutynin** (OROS technology) and tolterodine (membrane coated beads) in vitro and in vivo. STUDY DESIGN: In vitro studies were based on standardised dissolution experiments for each drug in media of different pH (artificial gastric fluid at pH 1.2, artificial intestinal fluid at pH 7.5, and water). In the two separate, identically designed in vivo studies, single doses of each drug were administered alone and with an antacid to male and female healthy volunteers aged 18-45 years. The randomised, crossover, open-label in vivo studies employed a validated assay to determine plasma concentrations of tolterodine and its metabolite 5-hydroxymethyl tolterodine (5-HM), or **oxybutynin** and its metabolite N-desethyloxybutynin. RESULTS: The in vitro study showed similar slow and steady drug release from ER-**oxybutynin** in each pH medium, with 64-71% released after 12 hours. Drug release from ER-tolterodine was steady and slow in artificial gastric fluid, with 72.5% of drug released after 12 hours. However, drug release was much faster in artificial intestinal fluid and water, where 69.8% and 69.1%, respectively, of the drug was released within 4 hours. These in vitro results were consistent with the findings of the in vivo studies. In vivo, the pharmacokinetic profile (peak **plasma concentration** [C(max)] and area under the concentration-time curve) of ER-**oxybutynin** was similar after administration with or without antacid, whereas C(max) values of both tolterodine and 5-HM increased significantly when ER-tolterodine was administered with antacid ($p < or = 0.017$ vs ER-tolterodine alone). CONCLUSIONS: Changes in pH affected the release of tolterodine from ER-tolterodine, while they had no effect on the release of **oxybutynin** from the proprietary ER technology used in ER-**oxybutynin**. The technology employed in ER formulations thus determines sensitivity of drug release to external factors.

L4 ANSWER 2 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2004166019 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15059046
TITLE: **Oxybutynin** extended-release: a review of its use

in the management of overactive bladder.

AUTHOR: Siddiqui M Asif A; Perry Caroline M; Scott Lesley J
CORPORATE SOURCE: Adis International Limited, Mairangi Bay, Auckland, New Zealand.. demail@adis.co.nz

SOURCE: Drugs, (2004) 64 (8) 885-912.
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: (EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 20040403
Last Updated on STN: 20041117
Entered Medline: 20041116

AB The OROS-based **oxybutynin** extended-release (ER) formulation (Lyrinel XL; Ditropan XL) represents a new form of oral delivery for **oxybutynin**, a muscarinic receptor antagonist used in the treatment of overactive bladder (OAB). The release of **oxybutynin** from **oxybutynin** ER occurs in a sustained manner, resulting in a smoother **plasma concentration**-time profile and a lower maximum **plasma concentration** than those seen with **oxybutynin** immediate-release (IR). The ER formulation has been developed with the aim of improving the tolerability of **oxybutynin** therapy and facilitating once-daily administration. Moreover, **oxybutynin** ER offers greater flexibility in dosage (5-30 mg/day) than the other available treatment options. At dosages of 5-30 mg once daily, **oxybutynin** ER produced significant decreases from baseline in weekly urinary urge incontinence in patients with OAB. In addition, there were significant decreases in weekly total incontinence episodes and micturition frequency. In two randomised, double-blind studies in patients with OAB, the improvement in all the symptoms with once-daily **oxybutynin** ER 5-30 mg/day was similar to that produced by **oxybutynin** IR 5-20 mg/day given one to four times daily. Once-daily **oxybutynin** ER 10 mg was superior to tolterodine IR 4 mg/day given as two daily doses and as effective as once-daily tolterodine ER 4 mg/day in decreasing urinary incontinence; the decreases in micturition frequency with **oxybutynin** ER were significantly greater than those seen with either of tolterodine formulations. **Oxybutynin** ER was well tolerated in all the trials, with adverse events usually being mild to moderate and transient. In direct comparisons, the overall tolerability profile of **oxybutynin** ER was better than that of **oxybutynin** IR. **Oxybutynin** ER was similar to tolterodine (IR and ER) with respect to the incidence of clinically important dry mouth. A large 12-month tolerability study demonstrated no significant risks associated with the long-term use of **oxybutynin** ER. A few noncomparative studies have shown promising results with **oxybutynin** ER in the treatment of adult and paediatric patients with neurogenic bladder dysfunction secondary to neuronal injury. Long- and short-term studies have reported significant improvements in health-related quality of life with **oxybutynin** ER therapy. In addition, pharmacoeconomic studies have suggested that **oxybutynin** ER is more cost effective than **oxybutynin** IR and at least as cost effective as tolterodine IR. In conclusion, **oxybutynin** ER shows excellent efficacy in the treatment of symptoms associated with OAB in adults and the elderly with a good tolerability profile over a prolonged period of use (12 months). The ER formulation of **oxybutynin** provides a smooth **plasma concentration** profile over the 24-hour dosage interval, facilitating once-daily administration. Hence, given its overall efficacy/tolerability profile and dosage flexibility, **oxybutynin** ER provides an excellent treatment option in the first-line pharmacotherapy of OAB.

L4 ANSWER 3 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2003529514 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14606931
TITLE: Clinical pharmacokinetics of drugs used to treat urge incontinence.
AUTHOR: Guay David R P
CORPORATE SOURCE: Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455, USA.. guyayx001@umn.edu
SOURCE: Clinical pharmacokinetics, (2003) 42 (14) 1243-85. Ref: 328
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20031111
Last Updated on STN: 20040318
Entered Medline: 20040317

AB Urge incontinence (also known as overactive bladder) is a common form of urinary incontinence, occurring alone or as a component of mixed urinary incontinence, frequently together with stress incontinence. Because of the pathophysiology of urge incontinence, anticholinergic/antispasmodic agents form the cornerstone of therapy. Unfortunately, the pharmacological activity of these agents is not limited to the urinary tract, leading to systemic adverse effects that often promote nonadherence. Although the pharmacokinetics of flavoxate, propantheline, scopolamine, imipramine/desipramine, trospium chloride and propiverine are also reviewed here, only for **oxybutynin** and tolterodine are there adequate efficacy/tolerability data to support their use in urge incontinence. **Oxybutynin** is poorly absorbed orally (2-11% for the immediate-release tablet formulation). Controlled-release oral formulations significantly prolong the time to peak **plasma concentration** and reduce the degree of fluctuation around the average concentration. Significant absorption occurs after intravesical (bladder) and transdermal administration, although concentrations of the active N-desethyl metabolite are lower after transdermal compared with oral administration, possibly improving tolerability. Food has been found to significantly affect the absorption of one of the controlled-release formulations of **oxybutynin**, enhancing the rate of drug release. **Oxybutynin** is extensively metabolised, principally via N-demethylation mediated by the cytochrome P450 (CYP) 3A isozyme. The pharmacokinetics of tolterodine are dependent in large part on the pharmacogenomics of the CYP2D6 and 3A4 isozymes. In an unselected population, oral bioavailability of tolterodine ranges from 10% to 74% (mean 33%) whereas in CYP2D6 extensive metabolisers and poor metabolisers mean bioavailabilities are 26% and 91%, respectively. Tolterodine is metabolised via CYP2D6 to the active metabolite 5-hydroxymethyl-tolterodine and via CYP3A to N-dealkylated metabolites. Urinary excretion of parent compound plays a minor role in drug disposition. Drug effect is based upon the unbound concentration of the so-called 'active moiety' (sum of tolterodine + 5-hydroxymethyl-tolterodine). Terminal disposition half-lives of tolterodine and 5-hydroxymethyl-tolterodine (in CYP2D6 extensive metabolisers) are 2-3 and 3-4 hours, respectively. Coadministration of antacid essentially converts the extended-release formulation into an immediate-release formulation. Knowledge of the pharmacokinetics of these agents may improve the treatment of urge incontinence by allowing the identification of individuals at high risk for toxicity with 'usual' dosages. In addition, the use of alternative formulations (controlled-release oral, transdermal) may also facilitate adherence, not only by reducing the frequency of drug administration but

also by enhancing tolerability by altering the proportions of parent compound and active metabolite in the blood.

L4 ANSWER 4 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2003396938 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12934778
TITLE: Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral **oxybutynin** administration in healthy subjects.
COMMENT: Comment in: Mayo Clin Proc. 2003 Jun;78(6):681-3. PubMed ID: 12934775
AUTHOR: Appell Rodney A; Chancellor Michael B; Zobrist R Howard; Thomas Heather; Sanders Steven W
CORPORATE SOURCE: Department of Urology, Baylor College of Medicine, Houston, Tex 77030, USA.. rappell@bcm.tmc.edu
SOURCE: Mayo Clinic proceedings, (2003 Jun) 78 (6) 696-702. Journal code: 0405543. ISSN: 0025-6196.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030826 Last Updated on STN: 20030828 Entered Medline: 20030827

AB OBJECTIVE: To compare the pharmacokinetics and adverse effect dynamics of 2 modified-release **oxybutynin** treatments. SUBJECTS AND METHODS: Between October 15 and November 6, 2001, 13 healthy subjects (7 men and 6 women) participated in a randomized, 2-way crossover study of transdermal (Oxytrol, 3.9 mg/d) and extended-release oral (Ditropan XL, 10 mg) **oxybutynin**. Multiple blood and saliva samples were collected. Pharmacokinetic parameters and total salivary output were assessed. Statistical analyses included 95% confidence intervals, paired t test, analysis of variance, and linear regression. RESULTS: Steady-state plasma concentrations were achieved after the first transdermal application and after the second extended-release oral dose. Mean +/- SD 24-hour **oxybutynin** areas under the concentration-time curve were comparable during transdermal and oral extended-release treatments, 10.8 +/- 24 vs 9.2 +/- 33 ng x h(-1) x mL(-1), respectively. However, the ratio of area under the curve (N-desethyloxybutynin/**oxybutynin**) after transdermal administration (1.2 +/- 03) was significantly lower ($P < .001$) than after extended-release oral administration (4.1 +/- 0.9). Mean plasma concentrations were less variable during transdermal compared with extended-release oral administration. Mean +/- SD saliva output was greater during transdermal than extended-release oral treatment (15.7 +/- 93 vs 12.2 +/- 6.8 g, respectively; $P = .02$). Lower N-desethyloxybutynin during transdermal application was associated with greater saliva output ($r = -059$, $P = .04$). No clinically important treatment-related adverse effects were observed. CONCLUSIONS: Transdermal **oxybutynin** administration results in greater systemic availability and minimizes metabolism to N-desethyloxybutynin compared with extended-release oral administration. Lower N-desethyloxybutynin **plasma concentration** and greater saliva output during transdermal treatment correspond to the reported low incidence of dry mouth in patients with overactive bladder.

L4 ANSWER 5 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2002291929 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12031836
TITLE: Extractionless and sensitive method for high-throughput quantitation of cetirizine in human plasma samples by liquid chromatography-tandem mass spectrometry.

AUTHOR: de Jager A D; Hundt H K L; Swart K J; Hundt A F; Els J
CORPORATE SOURCE: FARMOVS-PAREXEL-Bioanalytical Serviced Division, Private Bag X09, Brandhof 9324, Bloemfontein, South Africa.. andrew.dejager@farmovs-parexel.com
SOURCE: Journal of chromatography. B, Analytical technologies in the biomedical and life sciences, (2002 Jun 25) 773 (2) 113-8.
Journal code: 101139554. ISSN: 1570-0232.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020529
Last Updated on STN: 20020807
Entered Medline: 20020806

AB Following a single 10-mg oral dose of cetirizine dihydrochloride to 24 healthy volunteers, the analyte was quantified in human plasma. Protein precipitation using acetonitrile (ACN) was followed by reversed-phase liquid chromatography and tandem mass spectrometry. The MS/MS method was optimised using a PE Sciex API 2000 triple quadrupole mass spectrometer in selected reaction monitoring (SRM) mode, using electrospray with positive ionisation. **Oxybutynin** was used as the internal standard. The assay method represents a robust, high-throughput, highly specific and sensitive quantitative assay procedure, with 0.5 ng/ml being the lowest **plasma concentration** that could be reliably quantified.
The procedure involves minimal sample preparation, and is well suited to clinical studies of the drug involving large numbers of generated samples. Pre-dose as well as post-dose samples up to and including 48 h were quantified, and the data generated were used to determine the pharmacokinetic profile of the drug.

L4 ANSWER 6 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2001644316 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11696741
TITLE: Intravesical **oxybutynin**: mode of action assessed by passive diffusion and electromotive administration with pharmacokinetics of **oxybutynin** and N-desethyl **oxybutynin**.
COMMENT: Comment in: J Urol. 2001 Dec;166(6):2241. PubMed ID: 11696743
AUTHOR: Di Stasi S M; Giannantoni A; Navarra P; Capelli G; Storti L; Porena M; Stephen R L
CORPORATE SOURCE: Department of Urology, "Tor Vergata" University of Rome and Institutes of Pharmacology and Hygiene, Catholic University of Rome, Italy.
SOURCE: Journal of urology, (2001 Dec) 166 (6) 2232-6.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107
Last Updated on STN: 20020124
Entered Medline: 20011231

AB PURPOSE: A proportion of patients with detrusor hyperreflexia who are unresponsive to oral **oxybutynin** often benefit from intravesical **oxybutynin** instillation. To our knowledge the precise mode of action of this method is obscure. MATERIALS AND METHODS: In 12 patients with detrusor hyperreflexia who were previously unresponsive to oral and intravesical passive diffusion of 5 mg. **oxybutynin** we administered 5 mg. **oxybutynin** orally as well as increased doses of 15 mg. **oxybutynin** intravesically with passive diffusion and

with 15 mA. associated electric current. Each administration mode per patient was associated with an 8-hour urodynamic monitoring session during which **oxybutynin** and N-desethyl **oxybutynin** plasma levels, and intravesical **oxybutynin** uptake were measured. RESULTS: A dose of 5 mg. **oxybutynin** orally induced no urodynamic improvement with an area under the **plasma concentration** time curve of combined N-desethyl **oxybutynin** plus **oxybutynin** of 16,297 ng./8 hours and an area under the curve ratio of N-desethyl **oxybutynin**-to-**oxybutynin** of 11:1. Passive diffusion **oxybutynin** resulted in 12 mg. **oxybutynin** intravesical uptake and significant improvement in 3 of 8 urodynamic measurements, although the area under the curve of combined N-desethyl **oxybutynin** plus **oxybutynin** was only 2,123 ng./8 hours and the N-desethyl **oxybutynin**-to-**oxybutynin** ratio was 1.1:1.0. Electromotive administration of **oxybutynin** resulted in almost complete intravesical uptake of the 15 mg. dose, significant improvement in all 8 urodynamic measurements and an increased **oxybutynin** level versus oral and passive diffusion, although the area under the curve of combined N-desethyl **oxybutynin** plus **oxybutynin** was 4,574 ng./8 hours and the N-desethyl **oxybutynin**-to-**oxybutynin** ratio was inverted at 1.0:1.4. The oral dose of 5 mg. **oxybutynin** caused anticholinergic side effects in 8 of the 12 patients. Neither intravesical passive diffusion nor electromotive administration caused side effects with an uptake of 12 and 15 mg., respectively. CONCLUSIONS: A large proportion of intravesical **oxybutynin** is sequestered, probably in the urothelium. Intravesical **oxybutynin** administration confers therapeutic benefits via localized direct action within the bladder wall.

L4 ANSWER 7 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2000135425 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10672870
TITLE: Analysis of the electrophysiologic effects of short-term **oxybutynin** on guinea pig and rabbit ventricular cells.
AUTHOR: Jones S E; Kasamaki Y; Shuba L M; Ogura T; McCullough J R; McDonald T F
CORPORATE SOURCE: Department of Physiology and Biophysics, Dalhousie University, Halifax, Nova Scotia, Canada.
SOURCE: Journal of cardiovascular pharmacology, (2000 Feb) 35 (2) 334-40.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000313

AB The objective of this study was to investigate the cardioactive properties of **oxybutynin**, a drug that is widely prescribed for management of voiding dysfunction. Membrane currents were recorded from whole-cell-configured guinea pig ventricular myocytes, and action potentials were recorded from guinea pig and rabbit papillary muscles. L-type Ca2+ current (I(Ca),L), inward-rectifier K+ current (I(K1)), and delayed-rectifier K+ current (I(K)) were unaffected by < or = 1 microM **oxybutynin**, and inhibited by higher concentrations. The concentrations that reduced the currents to one-half of predrug control amplitude (K0.5) were as follows: 1(Ca),L, 16.1 microM, I(K1), 18.2 microM, rapidly activating I(K)(I(Kr)), 11.4 microM, and slowly activating I(K)(I(Ks)), 28.7 microM. Action-potential durations at 20 and 90% repolarization (APD20, APD90) were unaffected by **oxybutynin** < or =3 microM in guinea pig papillary muscles driven at 1 Hz; higher

concentrations selectively shortened the APD20 by as much as 25% (100 microM), and caused moderate reductions in maximal upstroke velocity. Changes in the action potentials of rabbit papillary muscles were even smaller than in the guinea pig muscles. Because the peak therapeutic **plasma concentration** of **oxybutynin** is in the 0.01-0.1 microM range, the results suggest that the drug is highly unlikely to have adverse effects on cardiac electrical activity.

L4 ANSWER 8 OF 10 MEDLINE on STN
ACCESSION NUMBER: 1999290398 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10363730
TITLE: An extended-release formulation of **oxybutynin** chloride for the treatment of overactive urinary bladder.
AUTHOR: Goldenberg M M
CORPORATE SOURCE: Mount Sinai NYU Health, New York, New York 10029, USA.
SOURCE: Clinical therapeutics, (1999 Apr) 21 (4) 634-42. Ref: 27
Journal code: 7706726. ISSN: 0149-2918.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990727
Last Updated on STN: 19990727
Entered Medline: 19990713

AB Detrusor instability, or urinary incontinence, is common in elderly patients, particularly elderly women. The clinical symptoms of overactive, or unstable, urinary bladder include urge urinary incontinence, urgency, and frequency. Mixed urinary incontinence, which comprises urge urinary incontinence and stress incontinence, is manifested by increased intraabdominal pressure on coughing or sneezing. The detrusor muscle of the bladder is under the control of the parasympathetic, or muscarinic, nervous system. The drug of choice in this condition is **oxybutynin** chloride, which has the ability to block acetylcholine released from parasympathetic nerves in the urinary bladder, preventing contractions of the muscle and exerting a direct spasmolytic effect on the bladder. A new extended-release oral tablet formulation, OROS **oxybutynin**, uses osmotic pressure to deliver the drug at a controlled rate over approximately 24 hours. It resembles a conventional tablet but has a two-part core consisting of a drug layer and below it, a "push" layer containing osmotically active components, the whole surrounded by a semipermeable membrane with a laser-drilled opening in the drug side. Water in the gastrointestinal tract enters the tablet and mixes with the drug to form a suspension. The "push" layer expands and pushes the suspended drug out of the orifice and into the gastrointestinal tract for eventual absorption. Pharmacokinetic studies have indicated a slow rise in mean **plasma concentration** of the isomer R-**oxybutynin** for 4 to 6 hours after a single dose of OROS **oxybutynin**, followed by maintenance of steady concentrations for up to 24 hours, minimizing the fluctuations between peak and trough associated with TID dosing of 5-mg immediate-release **oxybutynin** tablets. Efficacy and safety studies comparing the extended-release with the immediate-release formulation of **oxybutynin** demonstrated equivalent efficacy in patients with overactive urinary bladder. The adverse-event profile of **oxybutynin** is similar to that of a typical anticholinergic agent such as atropine--dry mouth, constipation, somnolence, blurred vision, headache, and gastrointestinal pain--although in 2 clinical studies, the incidence of dry mouth was less with the extended-release formulation. Once-daily dosing with OROS **oxybutynin** appears to be well tolerated and effective, as well as convenient, for the treatment of overactive bladder, particularly for elderly patients using multiple

medications.

L4 ANSWER 9 OF 10 MEDLINE on STN
ACCESSION NUMBER: 1999172984 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10073329
TITLE: Pharmacokinetics of an oral once-a-day controlled-release **oxybutynin** formulation compared with immediate-release **oxybutynin**.
AUTHOR: Gupta S K; Sathyan G
CORPORATE SOURCE: Alza Corporation, Palo Alto, CA, USA.
SOURCE: Journal of clinical pharmacology, (1999 Mar) 39 (3) 289-96. Journal code: 0366372. ISSN: 0091-2700.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990517 Last Updated on STN: 20011015 Entered Medline: 19990430

AB **Oxybutynin** is used for the treatment of urge urinary incontinence. In this randomized, open-label, two-way crossover, multiple-dose study, the pharmacokinetics of a once-daily, controlled-release formulation, OROS **oxybutynin** chloride, was compared with that of immediate-release (IR) **oxybutynin** (Ditropan). Thirteen healthy female volunteers received three 5 mg OROS **oxybutynin** chloride tablets once daily for 4 days or IR **oxybutynin** 5 mg administered every 8 hours for 4 days. On day 1, with OROS **oxybutynin** chloride, mean plasma concentrations rose slowly over approximately 6 hours following dosing (mean Cmax 4.2 ng/mL) and remained fairly constant over the 24-hour dosing interval, whereas with IR **oxybutynin**, mean plasma concentrations rose rapidly within the first hour after dosing (mean Cmax 12.0 ng/mL), then declined. The mean **oxybutynin** degree of fluctuation was much lower for OROS **oxybutynin** chloride (78%) than for IR **oxybutynin** (371%). For both formulations, the **plasma concentration** -time profiles for the metabolite N-desethyloxybutynin paralleled those of **oxybutynin** but at higher concentrations. Steady-state **oxybutynin** concentrations were achieved by day 3 for both formulations. Mean area under the concentration-time curve (AUC) values for both **oxybutynin** and its metabolite were similar between day 1 and day 4 for each treatment, suggesting time-invariant pharmacokinetics. With OROS **oxybutynin** chloride, mean relative bioavailability was higher (153%) for **oxybutynin** and lower (69%) for N-desethyloxybutynin compared with IR **oxybutynin**. This increased bioavailability may be due to reduced first-pass metabolism; within 3 to 5 hours after dosing, OROS systems are thought to reach the colon, where cytochrome P450-mediated oxidation (**oxybutynin**'s primary metabolic pathway) may be less extensive than in the small intestine. Fewer subjects reported any adverse event with OROS **oxybutynin** chloride than with IR **oxybutynin** (including dry mouth, **oxybutynin**'s most frequently reported anticholinergic adverse effect).

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AUTHOR: Buyse G; Waldeck K; Verpoorten C; Bjork H; Casaer P; Andersson K E

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AB PURPOSE: To unravel why intravesical **oxybutynin** is more effective and causes significantly fewer systemic side effects than oral **oxybutynin** in the treatment of neurogenic bladder dysfunction, we tested the hypothesis that the absorption and metabolism of **oxybutynin** are changed after intravesical instillation. MATERIALS AND METHODS: A high-performance liquid chromatography assay was developed for both **oxybutynin** and its active metabolite, N-desethyl-**oxybutynin**. Plasma concentrations were quantified after intravesical (n = 11) and oral (n = 5) administration of **oxybutynin** in children under steady-state conditions. Pharmacokinetic parameters were calculated. RESULTS: Oral administration of **oxybutynin** (0.2 mg./kg./dose) resulted in peak plasma concentrations for N-desethyl-**oxybutynin** which were 7.4 +/- 1.3 times higher than corresponding values for **oxybutynin** (n = 5). Also the AUC (area under the **plasma concentration** time curve) values were higher for N-desethyl-**oxybutynin** compared with those of **oxybutynin**, the ratio being 10.8 +/- 1.0 (n = 5). Intravesical instillation (0.2 mg./kg./dose), on the other hand, resulted in reduced metabolite generation and peak plasma concentrations for N-desethyl-**oxybutynin** which were in the same range as those for **oxybutynin**, the ratio being 1.2 +/- 0.1 (n = 11). The ratio for the AUC values for N-desethyl-**oxybutynin** and **oxybutynin** was 2.1 +/- 0.2 (n = 11). CONCLUSIONS: The significantly lower AUC ratio of the N-desethyl metabolite over the mother compound, due to a reduced first pass metabolism, may explain the clinically relevant reduction of side effects that characterizes intravesical compared with oral **oxybutynin** therapy.

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L5 0 L2 AND L3